PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Washington D.C. 20231
United States of America

in its capacity as elected Office

Date of mailing: 29 May 1995 (29.05.95)	
International application No.: PCT/EP94/03169	Applicant's or agent's file reference: JAB 948-PCT
International filing date: 22 September 1994 (22.09.94)	Priority date: 30 September 1993 (30.09.93)
Applicant: FRANÇOIS, Marc, Karel, Jozef et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

26 April 1995 (26.04.95)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

M.C. Taylor

Telephone No.: (41-22) 730.91.11

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

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NOTIFICATION CONCERNING DOCUMENT TRANSMITTED

To:

United States Patent and Trademark Office
(Box PCT)
Washington D.C. 20231
United States of America

in its capacity as elected Office

Date of mailing (day/month/year)	
19 December 1995 (19.12.95)	
International application No.	**International filing date** (day/month/year)
PCT/EP94/03169	22 September 1994 (22.09.94)
Applicant	
JANSSEN PHARMACEUTICA N.V. et al	

The International Bureau transmits herewith the following documents and number thereof:

_____ copy of the international preliminary examination report (Article 36(3)(a))

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

C. Boroli

Telephone No.: (41-22) 730.91.11

80

PATENT COOPERATION TREATY

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REC'D 18 DEC 1995
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
JAB 948-PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 94/ 03169	22/09/1994	30/09/1993
International Patent Classification (IPC) or national classification and IPC		
A61K31/495		
Applicant		
JANSSEN PHARMACEUTICA N.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This **REPORT** consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by **ANNEXES**, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consists of a total of _____ sheets.

3. This report contains indications and corresponding pages relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26/04/1995	15. 12. 95
Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	B. Isert Telephone No. 8651

Intern. application No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

PCT/EP94/03169

I. Basis of the report

1. This report has been drawn up on the basis of (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.):

[x] the international application as originally filed.

[ ] the description, pages _____, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____,

[ ] the claims, Nos. _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. _____, filed with the letter of _____,
Nos. _____, filed with the letter of _____,

[ ] the drawings, sheets/fig _____, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

[ ] the description, pages _____.
[ ] the claims, Nos. _____.
[ ] the drawings, sheets/fig _____.

3. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 2,6-9	YES
	Claims 1,3-5,10	NO
Inventive Step (IS)	Claims	YES
	Claims 2,6-9	NO
Industrial Applicability (IA)	Claims 1-10	YES
	Claims	NO

2. CITATIONS AND EXPLANATIONS

1). The following documents (D) cited in the Internationl search report are referred to in this communication:

D1= Antimicrob. Agents Chemotherap., 1992, 36(2):477-480
D2= WO -A- 9319061
D3= US -A- 4916134
D4 =Int. J. Pharmaceut. 1992, 80:253-258

1.1 Intermediate document D2 prejudical to claim 1 comprises itraconazole and saperconazole formulations with cyclodextrin possibly comprising polyethylene glycol (as stabilizer) and an acidic pH regulator. See D2, page 11 line 26 - page 13 line 25.

2). The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of Claims 1,3-5,10 is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT).

Said claims relate to an acidic (pH = 2.0) antifungal formulation (itraconazole, saperconazole) comprising cyclodextrin (hydroxypropyl-beta- cyclodextrin, HPCD) and an alcolic co-solvent (propylene glycol), as well as a method for its preparation.

D1 describes such oral formulations having a pH=2.0 comprising antifungal azoles (inter alia, itraconazole and saperconazole) solubilized in HPCD and propylene glycol. See D1, especially page 478, right column - page 479. It is noted that present claim 3 further specifies the cyclodextrin by a certain "M.S". It appears that the cyclodextrin used in D1 would meet that specification as it was obtained from the present applicant.

3). The present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject-matter of Claims 2,6-9 does not involve an inventive step (Rule 65(1)(2) PCT).

Said claims further specify the formulations with regard to the presence of sweeteners, flavors, and the amount of the components present in a formulation.

The use of sweeteners such as sodium saccharin and flavors (claims 2,6,7) in oral azole formulations is known from D3, wherein the azoles are dissolved in propylene glycol. See D3, examples 12 and 13, and column 9 line 35 - column 10 line 23.
Present claims 8 and 9 relate to compositions similar to that described in D1, which contains 2.5% azole (versus 4 or 1%) and 60% HPCD (versus 40% as to claim 9), but no sweeteners. The slightly different azole and HPCD contents are not considered inventive unless a particular effect is achieved. The use of sweeteners etc. is also obvious, as the present formulations are destined for use in patients, whereas the formulations of D1 were ad-

ministered to animals.

3.1 In view of D4 (see first complete paragraph at page 258) it appears that the present process of dissolving antifungal compounds (see claims 1,10) cannot be applied to any antifungal.

4). The claims 1-10 are industrially applicable as they relate to the preparation of medicaments (Article 33 (4) PCT).

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO-A-9319061	30.09.93	10.03.93	18.03.92

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

The documents D1,D2 and D4 have not been identified in the description nor as the relevant background art disclosed therein been discussed. The requirements of Rule 5.1(a)(ii) PCT are, thus, not fulfilled.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claim 1 is objected to under Article 6 PCT:

The term "sufficent amount of a cyclodextrin" used in claim 1 is unclear.
The term "antifungal" used in claim 1 appears to be too unspecific, see item 3.1 of the "reasoned statement" above. Note that in the present description only reference is made to azole compounds.

PATENT COOPERATION TREATY

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
JAB 948-PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 94/03169	22/09/94	30/09/93
Applicant		
JANSSEN PHARMACEUTICA N.V. et al.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:
   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 94/03169

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/495 A61K9/08 A61K47/40 A61K47/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ANTIMICROB. AGENTS CHEMOTHER., vol.36, no.2, February 1992 pages 477 - 480 J.S. HOSTETLER ET AL. 'Effect of cyclodextrin on the pharmacology of antifungal oral azoles' * see especially p. 478 right column - p. 479 left column *	1,3-5,10
Y	* " *	2,6
P,X	WO,A,93 19061 (JANSSEN) 30 September 1993 * see claims 1-3,5-12, p. 11 line 26 - p. 13 line 25 *	1
Y	US,A,4 916 134 (HEERES ET AL.) 10 April 1990 cited in the application * see especially examples 12 and 13 *	2,6

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 January 1995	10.02.95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Isert, B

Form PCT/ISA/210 (second sheet) (July 1992)

International Application No
PCT/EP 94/03169

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	INT. J. PHARMACEUT., vol.80, 1992 pages 253 - 258 J. PITHA ET AL. 'Preparation of drug: hydroxypropylcyclodextrin complexes by a method using ethanol or aqueous ammonium hydroxide as co-solubilizer' * see especially summary and p. 258 * -----	1

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 94/03169

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9319061	30-09-93	AU-B-	3632493	21-10-93
		CA-A-	2117651	30-09-93
		EP-A-	0631578	04-01-95
		FI-A-	944311	16-09-94
		NO-A-	943450	11-11-94
US-A-4916134	10-04-90	AU-B-	600107	02-08-90
		AU-A-	1358588	29-09-88
		DE-A-	3874576	22-10-92
		DK-B-	168336	14-03-94
		EP-A,B	0283992	28-09-88
		ES-T-	2044991	16-01-94
		JP-B-	6067929	31-08-94
		JP-A-	63277674	15-11-88
		SU-A-	1635900	15-03-91

08/604,950 Reamer 1205

PATENT COOPERATION TREATY

Copy for the Elected Office (EO/ US) 12C1 2/11/97

From the INTERNATIONAL BUREAU

PCT

To:

QUAGHEBEUR, Luc
Janssen Pharmaceutica N.V.
Patent Dept.
Turnhoutseweg 30
B-2340 Beerse
BELGIQUE

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year) 07 February 1996 (07.02.96)	
Applicant's or agent's file reference JAB 948-PCT	IMPORTANT NOTIFICATION
International application No. PCT/EP94/03169	International filing date (day/month/year) 22 September 1994 (22.09.94)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
FRANÇOIS, Marc, Karel, Jozef Valére Broekaertstraat 53 B-1090 Brussel Belgium	BE	BE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
FRANÇOIS, Marc, Karel, Jozef Foxemaatstraat 64 B-2920 Kalmthout Belgium		
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer M.C. Taylor
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 730.91.11

Form PCT/IB/306 (July 1992)

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/495, 9/08, 47/40, 47/10

A1

(11) International Publication Number: **WO 95/08993**

(43) International Publication Date: 6 April 1995 (06.04.95)

(21) International Application Number: PCT/EP94/03169

(22) International Filing Date: 22 September 1994 (22.09.94)

(30) Priority Data:
129,504 30 September 1993 (30.09.93) US

(60) Parent Application or Grant
(63) Related by Continuation
US 129,504 (CIP)
Filed on 30 September 1993 (30.09.93)

(71) Applicant *(for all designated States except US)*: JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: FRANÇOIS, Marc, Karel, Jozef [BE/BE]; Valére Broekaertstraat 53, B-1090 Brussel (BE). DRIES, Willy, Maria, Albert, Carlo [BE/BE]; Molenzijde 17, B-2330 Merksplas (BE).

(74) Agent: QUAGHEBEUR, Luc; Janssen Pharmaceutica N.V., Patent Dept., Turnhoutseweg 30, B-2340 Beerse (BE).

(81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, FI, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LV, MD, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: ORAL FORMULATIONS OF AN ANTIFUNGAL

(57) Abstract

The present invention concerns a formulation for oral administration comprising an antifungal, a sufficient amount of a cyclodextrin or a derivative thereof, an aqueous acidic medium as bulk liquid carrier and an alcoholic co-solvent. Addition of one or more pharmaceutically acceptable sweeteners and one or more pharmaceutically acceptable flavours thereto yields palatable oral formulations. A process of preparing such formulations and pharmaceutical dosage forms comprising said formulations.

ORAL FORMULATIONS OF AN ANTIFUNGAL

The present invention is concerned with novel compositions of antifungal agents which have low solubility in aqueous media, a process for preparing said compositions and pharmaceutical dosage forms for oral administration comprising said novel compositions.

The development of efficacious pharmaceutical compositions of azole antifungals such as for example, itraconazole and saperconazole, is hampered considerably by the fact that said antifungals are only very sparingly soluble in water. The solubility and bioavailability of said compounds can be increased by complexation with cyclodextrins or derivatives thereof as described in WO 85/02767 and US-4,764,604. Alternatively, strongly acidic formulations (pH $\leq$ 1.5) of itraconazole and saperconazole can be formed in which the active ingredients are partially dissolved. Obviously such strongly acidic formulations are useless for oral administration. Aqueous formulations comprising a co-solvent such as PEG 400 completely dissolve itraconazole at pH 2.3 -2.5. However, these acidic formulations have problems with regard to ease-of-preparation, acceptability, palatability and especially bioavailability : upon administration said formulations can precipitate irreversibly, e.g. in the stomach. Acidic formulations comprising cyclodextrin or a derivative thereof might appear an obvious alternative, but the mere combinations prove to suffer from a number of similar problems, in particular difficulty-of-preparation, lack of stability (shelf life) and palatability, and unreliable absorption. In short, there still exists an important demand for easily prepared formulations of antifungal agents with good bioavailability and acceptable organoleptic properties for oral administration.

The present invention relates to formulations for oral administration which comprise an antifungal, e.g. itraconazole or saperconazole, as active ingredient, a sufficient amount of a cyclodextrin or a derivative thereof as a solubilizer, an aqueous acidic medium as bulk liquid carrier and an alcoholic co-solvent that greatly simplifies the preparation of the composition. Preferred formulations are rendered more palatable by adding one or more pharmaceutically acceptable sweeteners, and one or more pharmaceutically acceptable flavours.

A low-dosage formulation according to the present invention is suitable for treating patients suffering from fungal infections, particularly for treating AIDS patients with oral candidiasis infections. The need for reliable formulations of itraconazole (and saperconazole) in this indication is especially high because of resistance to fluconazole developing in *Candida* strains. Generally, 400 mg/day represents the minimum dose required to obtain meaningful plasm levels. Suitable oral formulations typically comprise from about 0.5% to about 1.5% (w/v), preferably about 1% (w/v) of the active ingredient.

A high-dosage formulation according to the present invention is suitable for treating patients suffering from systemic fungal infections. Suitable oral formulations for combatting systemic fungal infections typically comprise from about 3% to about 5%, preferably about 4% (w/v) of the active ingredient.

The formulations of the present invention are also suitable for the treatment of fungal infections in non-human animals, in particular for the treatment of dermatophytoses.

Itraconazole or (±)-cis-4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3H-1,2,4-triazol-3-one, is a broadspectrum antifungal compound developed for oral, parenteral and topical use and is disclosed in US-4,267,179. Its difluoro analog, saperconazole or (±)-cis-4-[4-[4-[4-[[2-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]-phenyl]-2,4-dihydro-2-(1-methoxypropyl)-3H-1,2,4-triazol-3-one, has improved activity against *Aspergillus* spp. and is disclosed in US-4,916,134.

Appropriate cyclodextrin derivatives are α-, β-, γ-cyclodextrins or ethers and mixed ethers thereof wherein one or more of the hydroxy groups of the anhydroglucose units of the cyclodextrin are substituted with C_{1-6}alkyl, particularly methyl, ethyl or isopropyl; hydroxyC_{1-6}alkyl, particularly hydroxyethyl, hydroxypropyl or hydroxybutyl; carboxyC_{1-6}alkyl, particularly carboxymethyl or carboxyethyl; C_{1-6}alkylcarbonyl, particularly acetyl; C_{1-6}alkyloxycarbonylC_{1-6}alkyl or carboxyC_{1-6}alkyloxyC_{1-6}alkyl, particularly carboxymethoxypropyl or carboxyethoxypropyl; C_{1-6}alkylcarbonyloxyC_{1-6}alkyl, particularly 2-acetyloxypropyl. Especially noteworthy as complexants and/or solubilizers are β-CD, 2,6-dimethyl-β-CD, 2-hydroxyethyl-β-CD, 2-hydroxyethyl-γ-CD, 2-hydroxypropyl-γ-CD and (2-carboxymethoxy)propyl-β-CD, and in particular 2-hydroxypropyl-β-CD.

The term mixed ether denotes cyclodextrin derivatives wherein at least two cyclodextrin hydroxy groups are etherified with different groups such as, for example, hydroxypropyl and hydroxyethyl.

The average molar substitution (M.S.) is used as a measure of the average number of moles of alkoxy units per mole of anhydroglucose. In the cyclodextrin derivatives for use in the compositions according to the present invention the M.S. is in the range of 0.125 to 10, in particular of 0.3 to 3, or from 0.3 to 1.5. Preferably the M.S. ranges from about 0.3 to about 0.8, in particular from about 0.35 to about 0.5 and most particularly is about 0.4. M.S. values determined by NMR of IR preferably range from 0.3 to 1, in particular from 0.55 to 0.75.

The average substitution degree (D.S.) refers to the average number of substituted hydroxyls per anhydroglucose unit. In the cyclodextrin derivatives for use in the compositions according to the present invention the D.S. is in the range of 0.125 to 3, in particular of 0.2 to 2 or from 0.2 to 1.5. Preferably the D.S. ranges from about 0.2 to about 0.7, in particular from about 0.35 to about 0.5 and most particularly is about 0.4. D.S. values determined by NMR of IR preferably range from 0.3 to 1, in particular from 0.55 to 0.75.

More particular β– and γ-cyclodextrin hydroxyalkyl derivatives for use in the compositions according to the present invention are partially substituted cyclodextrin derivatives wherein the average degree of alkylation at hydroxyl groups of different positions of the anhydroglucose units is about 0% to 20% for the 3 position, 2% to 70% for the 2 position and about 5% to 90% for the 6 position. Preferably the amount of unsubstituted β- or γ-cyclodextrin is less than 5% of the total cyclodextrin content and in particular is less than 1.5%. Another particularly interesting cyclodextrin derivative is randomly methylated β-cyclodextrin.

Most preferred cyclodextrin derivatives for use in the present invention are those partially substituted β-cyclodextrin ethers or mixed ethers having hydroxypropyl, hydroxyethyl and in particular 2-hydroxypropyl and/or 2-(1-hydroxypropyl) substituents.

The most preferred cyclodextrin derivative for use in the compositions of the present invention is hydroxypropyl-β-cyclodextrin having a M.S. in the range of from 0.35 to 0.50 and containing less than 1.5% unsubstituted β-cyclodextrin. M.S. values determined by NMR or IR preferably range from 0.55 to 0.75.

Substituted cyclodextrins can be prepared according to procedures described in US-3,459,731, EP-A-0,149,197, EP-A-0,197,571, US-4,535,152, WO-90/12035 and GB-2,189,245. Other references describing cyclodextrins for use in the compositions according to the present invention, and which provide a guide for the preparation, purification and analysis of cyclodextrins include the following : "Cyclodextrin Technology" by József Szejtli, Kluwer Academic Publishers (1988) in the chapter Cyclodextrins in Pharmaceuticals; "Cyclodextrin Chemistry" by M.L. Bender et al., Springer-Verlag, Berlin (1978); "Advances in Carbohydrate Chemistry", Vol. 12 Ed. by M.L. Wolfrom, Academic Press, New York (157) in the chapter The Schardinger Dextrins by Dexter French at p. 189-260; "Cyclodextrins and their Inclusions Complexes" by J. Szejtli, Akademiai Kiado, Budapest, Hungary (1982); I. Tabushi in Acc. Chem. Research, 1982, 15, p. 66-72; W. Sanger, Angewandte Chemie, 92, p. 343-361 (1981); A. P. Croft and R. A. Bartsch in Tetrahedron, 39, p. 1417-1474 (1983); Irie et al. Pharmaceutical Research, 5, p. 713-716, (1988); Pitha et al. Int. J. Pharm. 29, 73, (1986); DE 3,118,218; DE-3,317,064; EP-A-94,157; US-4,659,696; and US-4,383,992. The low-dosage oral formulations according to the present invention typically comprise from about 20% to about 60% (w/v), preferably about 40% (w/v) of the cyclodextrin. The high-dosage formulations typically comprise from about 50% to about 80% (w/v), preferably about 60% (w/v) of the cyclodextrin derivative.

In order to increase the rate of dissolution of the poorly soluble antifungal during the manufacturing process, an alcoholic co-solvent is employed in the formulations according to the present invention. For this purpose, preference is given to those alcoholic co-solvents that have good dissolving power for itraconazole and/or saperconazole, in particular ethanol, propylene glycol and glycerol, especially propylene glycol. Without the alcoholic co-solvent, the dissolution of itraconazole or saperconazole in an aqueous acidic cyclodextrin medium is very slow, requiring a viscous suspension to be stirred for a prohibitively long time until complete dissolution is obtained. Addition of the alcoholic co-solvent, in the range of about 1% (v/v) to about 20% (v/v), preferably about 10% (v/v), increases the dissolution rate of the antifungal agent in an aqueous acidic cyclodextrin medium by a factor of at least 5 (when used at 10% (v/v)) and thus considerably shortens and simplifies the production process.

As a bulk liquid carrier there is used an acidic aqueous medium. Preferably the acidity of said carrier derives from a strong, pharmaceutically acceptable acid such as hydrochloric acid. The bioavailability of the antifungal agent and the organoleptic properties of the oral formulations are affected contrariwise by the acidity. An optimum effect can be

obtained at pH 2.0 ± 0.1 : that is, at this pH value, a sufficiently stable and bioavailable antifungal formulation is obtainable, the organoleptic properties of which can be rendered acceptable.

Not surprisingly, the ingredients thus far described yield a fairly strong-tasting potion when mixed with one another. Besides the acid taste due to the low pH, a bitter taste originating from the active ingredient, and possibly from the co-solvent (e.g. in the case of propylene glycol), is also present. Optimum taste masking can be obtained by the use of two types of adjuvants, namely pharmaceutically acceptable sweeteners and flavours. Sweeteners are the more important additives in the low-dosage formulations, whereas the flavours are more important in the high-dosage formulations.

The pharmaceutically acceptable sweeteners comprise preferably at least one intense sweetener such as saccharin, sodium or calcium saccharin, aspartame, acesulfame potassium, sodium cyclamate, alitame, a dihydrochalcone sweetener, monellin, stevioside or sucralose (4,1',6'-trichloro-4,1',6'-trideoxy*galacto*sucrose), preferably saccharin, sodium or calcium saccharin, and optionally a bulk sweetener such as sorbitol, mannitol, fructose, sucrose, maltose, isomalt, glucose, hydrogenated glucose syrup, xylitol, caramel or honey.

The intense sweetener is conveniently employed in low concentrations. For example, in the case of sodium saccharin, the concentration may range from 0.04% to 0.1% (w/v) based on the total volume of the final formulation, and preferably is about 0.06% in the low-dosage formulations and about 0.08% in the high-dosage ones. The bulk sweetener can effectively be used in larger quantities ranging from about 10% to about 35%, preferably from about 10% to 15% (w/v). In the high-dosage formulations the cyclodextrin derivative behaves as a bulk sweetener and none of the aforementioned bulk sweeteners needs to be added.

The pharmaceutically acceptable flavours which can mask the bitter tasting ingredients in the low-dosage formulations are preferably fruit flavours such as cherry, raspberry, black currant or strawberry flavour. A combination of two cherry flavours was found to yield very good results in an itraconazole formulation both as regards physico-chemical stability as well as regards organoleptic acceptability. In the high-dosage formulations stronger flavours are required such as Caramel Chocolate flavour, Mint Cool flavour, Fantasy flavour and the like pharmaceutically acceptable strong flavours. Each flavour may be present in the final composition in a concentration ranging from 0.05% to 1%

(w/v). Combinations of said strong flavours are advantageously used. Preferably a flavour is used that does not undergo any change or loss of taste and colour under the acidic conditions of the formulation.

A preferred high-dosage formulation according to the present invention comprises by weight or by volume based on the total volume of the formulation :

(a) 4% (w/v) itraconazole;
(b) 60% (w/v) hydroxypropyl-β-cyclodextrin;
(c) 10% (v/v) propylene glycol;
(d) acid and base to adjust the pH of the composition within the range of 2.0 ± 0.1;
(e) 0.08% (w/v) sodium saccharin;
(f) up to 1% (w/v) of one or more strong flavours; and
(g) water.

The preparation of the formulations according to the present invention will hereafter be described with regard to a preferred low-dosage formulation having the following composition (% are by weight or by volume based on the total volume of the formulation) :

(a) 1% (w/v) itraconazole;
(b) 40% (w/v) hydroxypropyl-β-cyclodextrin;
(c) 10% (v/v) propylene glycol;
(d) acid and base to adjust the pH of the composition within the range of 2.0 ± 0.1;
(e) 0.06% (w/v) sodium saccharin;
(f) 19% (v/v) sorbitol (70%) non-crystallizing solution;
(g) up to 1% (w/v) of one or more cherry flavours; and
(h) water.

Optionally, the above preferred low-dosage formulation further comprises up to 0.1%, in particular 0.02% caramel sweetener.

Similar formulations can be prepared with saperconazole, though other flavours may be preferred then.

Said process of preparation comprises the steps of

(a) dissolving the active ingredient in the alcoholic co-solvent and acid;
(b) dissolving the cyclodextrin in water and adding thereto the solution prepared in (a) while stirring until homogenous;

(c) adding the sweetener(s) and the flavour(s);

(d) adjusting the acidity to pH 2.0 ± 0.1 and

(e) diluting the formulation to the desired end-volume.

In particular, for preparing 1 litre of the aforementioned preferred formulation 100 ml of propylene glycol is treated with 3.76 ml concentrated HCl, stirred and slightly heated. 10 g itraconazole is added and stirring is continued until homogeneous.
In a separate vessel, 400 g hydroxypropyl-β-cyclodextrin is dissolved in 400 ml distilled water. The solution of the active ingredient is added slowly to the cyclodextrin solution while stirring. The sorbitol solution (190 ml) is added and stirred till homogeneous. The sodium saccharin (0.6 g) is dissolved in 50 ml distilled water and added to the mixture. The flavours are added and the pH of the mixture (about 1.7) is adjusted with a 10 N NaOH solution to pH 2.0 ± 0.1. The resulting solution is diluted with distilled water to an end volume of 1 litre. A pharmaceutical dosage form is obtained by filtering the previous solution and filling it into suitable containers. e.g. in 100 ml glass bottles with a screw cap. The pharmaceutical dosage form advantageously comprises a minimal volume of air above the solution, preferably an inert gas such as nitrogen. Besides the exclusion of air (oxygen), storage at temperatures below 25°C also beneficially affects the maximum shelf life of the formulation for oral administration.

In case a more simple formulation lacking the flavour(s) and/or sweetener(s) is envisaged, step (c) is omitted partially or completely from the process of preparation.

Claims

1. A formulation for oral administration comprising an antifungal, a sufficient amount of a cyclodextrin or a derivative thereof, an aqueous acidic medium as bulk liquid carrier and an alcoholic co-solvent.

2. A formulation according to claim 1 further comprising one or more pharmaceutically acceptable sweeteners and one or more pharmaceutically acceptable flavours.

3. A formulation according to claim 1 or 2 wherein the antifungal is itraconazole or saperconazole and the cyclodextrin is hydroxypropyl-β-cyclodextrin having an M.S. in the range of 0.35 to 0.50 and containing less than 1.5% unsubstituted β-cyclodextrin.

4. A formulation according to claim 3 wherein the alcoholic co-solvent is propylene glycol.

5. A formulation according to claim 4 having a pH of 2.0 ± 0.1.

6. A formulation according to claim 5 wherein the pharmaceutically acceptable sweetener comprises at least one intense sweetener and optionally a bulk sweetener.

7. A formulation according to claim 6 wherein the intense sweetener is selected from the group consisting of saccharin, sodium or calcium saccharin and the bulk sweetener is selected from the group consisting of sorbitol, mannitol, fructose, sucrose, maltose, glucose, caramel or honey.

8. A formulation according to claim 2 comprising by weight or by volume based on the total volume of the formulation :
   (a) 4% (w/v) itraconazole;
   (b) 60% (w/v) hydroxypropyl-β-cyclodextrin;
   (c) 10% (v/v) propylene glycol;
   (d) acid and base to adjust the pH of the composition within the range of 2.0 ± 0.1;
   (e) 0.08% (w/v) sodium saccharin;
   (f) up to 1% (w/v) of one or more flavours; and
   (g) water.

9. A formulation according to claim 2 comprising by weight or by volume based on the total volume of the formulation :
   (a) 1% (w/v) itraconazole or saperconazole;
   (b) 40% (w/v) hydroxypropyl-β-cyclodextrin;
   (c) 10% (v/v) propyleneglycol;
   (d) acid or base to adjust the pH of the composition within the range of 2.0 ± 0.1;
   (e) 0.06% (w/v) sodium saccharin;
   (f) 19% (v/v) sorbitol (70%) non-crystallizing solution;
   (g) up to 1% (w/v) of one or more flavours;
   (h) 0.02% (w/v) of a caramel sweetener; and
   (i) water.

10. A process of preparing a formulation as claimed in claim 1, characterized in that said process comprises the steps of :
   (a) dissolving the active ingredient in the alcoholic co-solvent and acid;
   (b) dissolving the cyclodextrin in water and adding thereto the solution prepared in (a) while stirring until homogenous;
   (c) adding the sweetener(s) and the flavour(s), if any;
   (d) adjusting the acidity to pH 2.0 ± 0.1 and
   (e) diluting the formulation to the desired end-volume.

INTERNATIONAL SEARCH REPORT

[illegible]nat Application No
[illegible]CT/EP 94/03169

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/495 A61K9/08 A61K47/40 A61K47/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ANTIMICROB. AGENTS CHEMOTHER., vol.36, no.2, February 1992 pages 477 - 480 J.S. HOSTETLER ET AL. 'Effect of cyclodextrin on the pharmacology of antifungal oral azoles' * see especially p. 478 right column - p. 479 left column *	1,3-5,10
Y	* " *	2,6

P,X	WO,A,93 19061 (JANSSEN) 30 September 1993 * see claims 1-3,5-12, p. 11 line 26 - p. 13 line 25 *	1

Y	US,A,4 916 134 (HEERES ET AL.) 10 April 1990 cited in the application * see especially examples 12 and 13 *	2,6

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	INT. J. PHARMACEUT., vol.80, 1992 pages 253 - 258 J. PITHA ET AL. 'Preparation of drug: hydroxypropylcyclodextrin complexes by a method using ethanol or aqueous ammonium hydroxide as co-solubilizer' * see especially summary and p. 258 * -----	1

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[redacted]nation on patent family members

[redacted]nal Application No
[redacted]T/EP 94/03169

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